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While your PAH patients skip by, don't forget to check their rhythm . . .

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Clinicians who treat pulmonary hypertension (PH) have learned, often the hard way by direct observation, that atrial fibrillation, and atrial dysrhythmias in general, are poorly tolerated by their patients. It has long been recognized that atrial arrhythmias (AAs) are simultaneously associated with functional decline while also being a marker of a worsening clinical status in patients with left ventricular dysfunction from heart failure.[1] By virtue of its relative rarity, the interaction between AAs and PH is less well studied but still recognized as an ominous combination.[2] Additionally, unlike the well-recognized left atrial-pulmonary vein interactions in patients with left-sided heart disease, the cause for many AAs in those with pre-capillary PH in the absence of left-sided disease, is not well understood.[3] However, several studies involving animal models suggest that attenuating the abnormal sympathetic response in this condition may allow for AA inhibition.[4]

This issue of *Pulmonary Circulation* features an article from Valentina Mercurio and the group from Johns Hopkins on their center's experience with AAs in patients with pulmonary arterial hypertension (PAH) entitled "Pulmonary arterial hypertension and atrial arrhythmias: incidence, risk factors, and clinical impact."[5] Impressively, they looked at over 300 patients with PAH in a 16-year period, of whom the general characteristics were in keeping with most PAH patient populations seen in Western countries. The overall population was predominantly female at about 80%, and although it was somewhat disproportionately skewed towards PAH associated with connective tissue disease (PAH-CTD)[6] due to local referral patterns, this provides some important information in this population specifically; that is, in addition to the aforementioned association with adrenergic causes for AA, atrial fibrosis has also been invoked as a potential cause and we know that Liao et al. have reported this finding via a PDGF-A-mediated effect in a mouse model.[7] Furthermore, it is interesting that their population that went on to develop AAs had significantly increased filling pressures at baseline (right atrial pressure = 8.9 mmHg vs. 12.3 mmHg, pulmonary capillary wedge pressure = 10.3 mmgHg vs. 12.4 mmgHg) and a trend toward lower cardiac output and higher pulmonary vascular resistance. Again, this may simply represent a sicker or more advanced disease state patient group at baseline or may provide some insight into which populations are at risk for the development of AAs.

The authors provide two new and unique observations in patients with PAH-CTD. First, despite previously published data that AAs raise the overall risk profiles of PAH patients, the authors demonstrate that this distinction does not appear to carry over to the subset of PAH-CTDs; that is to say AAs do not appear to have any significant bearing on the outcomes of patients in this group. Second, in those with idiopathic PAH (IPAH), there is significant hazard in the development of AAs to the extent that the group's mortality climbs to be statistically commensurate with that of PAH-CTD. If this is effect is indeed being driven more by atrial fibrosis, AAs may, as in those with left-sided disease, serve as an important marker of worsening function in IPAH patients. This may warrant further investigation.

Anticoagulation remains an important and somewhat contentious issue in patients with PAH. It has been previously demonstrated that PAH-CTD patients have an increased risk of adverse events when being anticoagulated compared to the rest of the PAH cohort.[8] That being said, the stroke risk in patients with AAs and atrial fibrillation/flutter specifically is not clearly defined in the PAH subgroup. Although the benefit of anticoagulation in patients has very clearly and repeatedly been shown in patients with atrial fibrillation, the populations studied were most definitely of a left-sided etiology.[9] It would be hard to imagine that few if any clinicians would advocate leaving these PAH patients without anticoagulation, but it should be noted that the data supporting benefit in this group is relatively lacking in this subgroup. Rather, a real possibility exists that in those with AAs and PAH-CTD as the likely causative etiology, there is as yet an undetermined chance of harm with anticoagulation. Again, this is an area requiring further exploration.

The group led by Mercurio et al. in this study also make a very important observation in the relationship between

thyroid disease and AAs. The relationship between thyroid disease and PAH and AAs severally is well-described.[10] This paper makes it very clear that the combination of thyroid disease and PAH dramatically increases the risk of AAs compared to those with AAs from a presumed left-sided etiology. Even when comparing the combination of left heart disease and thyroid disease, this group appears to have a dramatically elevated risk for AAs. Clearly, we may have underestimated the morbidity associated with PAH patients who have thyroid disease!

The occurrence of AAs in patients with PAH has again been shown to have a clearly deleterious effect. The work by this Italian and American group highlights the effects not only in PAH patients as a whole but also serves to highlight the differential effects between IPAH and PAH-CTD along with also making important hemodynamic and metabolic contributions to the growing body of knowledge on this topic. Hopefully, these important findings will spur on other groups and allow for collaboration both on the identification and management of this special population.

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